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Human infection with *Strongyloides stercoralis* and other related Strongyloides species

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SUMMARY

The majority of the 30–100 million people infected with *Strongyloides stercoralis*, a soil transmitted intestinal nematode, have subclinical (or asymptomatic) infections. These infections are commonly chronic and longstanding because of the autoinfective process associated with its unique life cycle. A change in immune status can increase parasite numbers, leading to hyperinfection syndrome, dissemination, and death if unrecognized. Corticosteroid use and HTLV-1 infection are most commonly associated with the hyperinfection syndrome. *Strongyloides* adult parasites reside in the small intestine and induce immune responses both local and systemic that remain poorly characterized. Definitive diagnosis of *S. stercoralis* infection is based on stool examinations for larvae, but newer diagnostics – including new immunoassays and molecular tests – will assume primacy in the next few years. Although good treatment options exist for infection and control of this infection might be possible, *S. stercoralis* remains largely neglected.

Keywords

Strongyloidiasis; *Strongyloides stercoralis*; autoinfection; hyperinfection; anthelmintic therapy; corticosteroids

INTRODUCTION

Strongyloidiasis, the disease caused by the infection with *Strongyloides stercoralis*, and to a lesser extent by *Strongyloides fuelleborni fuelleborni* and *S. fuelleborni kelleyi*, is a soil-transmitted helminthiasis with an estimated 30–100 million people infected worldwide (Genta, 1989; Schar *et al.* 2013). Although the burden of the disease has been felt to be underestimated (Viney and Lok, 2007; Olsen *et al.* 2009; Schar *et al.* 2015, 2014), *S. stercoralis* infections in humans range from asymptomatic light infections to chronic symptomatic strongyloidiasis. However, uncontrolled multiplication of the parasite (hyperinfection) and potentially life-threatening dissemination of larvae in immunocompromised patients result in mortality rates of up to 85% (Keiser and Nutman, 2004; Mejia and Nutman, 2012).

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The parasite, occurring naturally in dogs, primates and humans, is endemic to the tropics and subtropics; foci of infection occur in temperate regions as well (Genta, 1989; Schar *et al.* 2013) where poor sanitation or other factors facilitate the transmission through fecal contamination. In parts of Africa and in Papua New Guinea, human infections caused by *S. fuelleborni fuelleborni* and *S. fuelleborni kelleyi* respectively have been reported (Pampiglione and Ricciardi, 1971; Hira and Patel, 1977; Vince *et al.* 1979; Crouch and Shield, 1982; Evans *et al.* 1991; Freedman, 1991; Ashford *et al.* 1992). In Africa, *S. fuelleborni fuelleborni* is primarily a parasite of primates, but in Papua New Guinea no animal host has been demonstrated for *S. fuelleborni kelleyi* (Ashford *et al.* 1992; Viney and Lok, 2007).

Strongyloides stercoralis is unique among nematodes infectious for humans in that larvae passing in the feces can give rise to a free-living generation of worms which, in turn, give rise to infective larvae. This so-called heterogonic development process serves as an amplification mechanism that allows for increased numbers of infective larvae in the external environment. The infective larvae are active skin penetrators; infection *per os*, while possible, is probably of limited importance. Because the parasitic female's eggs hatch often within the gastrointestinal tract, the potential for autoinfection exists when precociously developing larvae attain infectivity while still in the host. When the rate of autoinfection escapes control by the host, massive repenetration and larval migration may result.

LIFE CYCLE

The *S. stercoralis* (and *S. fuelleborni* spp.) life cycle encompasses both free-living and parasitic stages. Adult female worms parasitizing the human small intestine lay eggs in the intestinal mucosa that hatch into rhabditiform larvae, which are shed in the stool. In the environment, under warm moist conditions that often characterize the tropical and subtropical endemic areas, rhabditiform larvae can either moult into infective filariform larvae or develop through succeeding rhabditiform stages into free-living adults. Sexual reproduction occurs exclusively in the free-living stage.

Humans are generally infected transcutaneously, although infection has also been experimentally induced by oral administration of water contaminated with filariform larvae (Grove, 1996). After dermal penetration, the filariform larvae, through undefined mechanisms, migrate to the small intestine. The most clinically relevant, though perhaps not the predominant (Mansfield *et al.* 1996), migration is the classic pulmonary route, in which organisms enter the bloodstream and are carried to the lungs, ascending the tracheobronchial tree to enter the gastrointestinal tract. Only female adults are detectable in humans and subsequent reproduction occurs asexually through parthenogenesis (Neva, 1986).

Some rhabditiform larvae transform into invasive filariform larvae before being excreted. As such, they are capable of re-infecting the host by invading the intestinal wall or the perianal skin (Grove, 1996). This autoinfective cycle can occur at a low level throughout infection and allows subsequent generations to persist in the host indefinitely (Neva, 1986).

In the immunocompetent host, it is felt that cellular immune effector mechanisms and intrinsic parasite biology both serve to regulate the population density of adult worms in the intestine. With an alteration in host immune responsiveness, even one adult female can multiply rapidly by parthenogenesis, leading to accelerated autoinfection and/or dissemination.

EPIDEMIOLOGY

While endemic to the tropics and subtropics, foci of infection occur in temperate regions such as Japan, Italy, Australia and the USA (Genta, 1989; Al-Hasan *et al.* 2007; Schar *et al.* 2013). Immigrants and refugees comprise a significant population at risk for strongyloidiasis in high- and middle-income countries (Posey *et al.* 2007; Schar *et al.* 2013).

Prevalence and global distribution

There is little consensus about prevalence rates and the global distribution of human infections with *S. stercoralis*. There is, however, a great degree of consensus about the fact that the prevalence of strongyloidiasis has long been underestimated (Olsen *et al.* 2009; Schar *et al.* 2013; Khieu *et al.* 2014; Toledo *et al.* 2015). Although prevalence and global distribution patterns have been recently examined, aggregated detailed distribution maps and country by country data [cf. (Schar *et al.* 2013; Toledo *et al.* 2015)] are beyond the scope of this review

Transmission

While *Strongyloides* is most commonly acquired transcutaneously, high prevalence rates in institutionalized subjects raise speculation about alternate routes of transmission (Yoeli *et al.* 1972; Gatti *et al.* 2000; Robson *et al.* 2009). A Japanese study found support to this claim by observing a higher prevalence of *Strongyloides* infection in patients with *Blastocystis hominis*, a protozoan acquired by the fecal oral route (Czachor and Jonas, 2000). However, standard rather than strict contact precautions appear sufficient for prevention of nosocomial transmission based on case reports of patients with disseminated disease (Sugiyama *et al.* 2006). Transmission of *Strongyloides* infection after transplantation of kidneys, pancreatic allograft or intestines has been suggested by several reports where donors but not recipients had a history of travel to a *Strongyloides* endemic regions of the world (Ben-Youssef *et al.* 2005; Said *et al.* 2007; Patel *et al.* 2008) (see section below).

CLINICAL MANIFESTATIONS

Acute Strongyloidiasis

The clinical manifestations of acute strongyloidiasis are associated with the path of larval migration to the small intestine. Infected individuals may experience irritation at the site of skin penetration by larvae followed occasionally by localized oedema or urticaria. Within a week following infection, a dry cough and/or tracheal irritation may occur. Gastrointestinal symptoms such as diarrhoea, constipation, abdominal pain, or anorexia can occur (Keiser and Nutman, 2004) following the establishment of the infection in the small intestine.

Chronic Strongyloidiasis

Chronic infection with *S. stercoralis* is most often clinically asymptomatic (Grove, 1989). Since up to 75% of persons may have peripheral eosinophilia or elevated IgE levels (Rossi *et al.* 1993), *Strongyloides* should be considered in the differential diagnosis of high grade and/or persistent eosinophilia in travellers or expatriates from endemic areas (O'Connell and Nutman, 2015).

Symptomatic individuals may complain of diarrhoea, constipation, intermittent vomiting or borborygmus. Dermatologic manifestations such as recurrent urticaria can occur (Leighton and MacSween, 1990) as can *larva currens* (pruritic linear streaks located along the lower trunk, thighs and buttocks) as a result of migrating larvae (Pelletier, 1984; Pelletier and Gabre-Kidan, 1985; Grove, 1996). Unusual manifestations of chronic strongyloidiasis include arthritis (Richter *et al.* 2006); nephrotic syndrome (Hsieh *et al.* 2006), chronic malabsorption (Atul *et al.* 2005), duodenal obstruction (Harish *et al.* 2005; Suvarna *et al.* 2005), focal hepatic lesions (Gulbas *et al.* 2004) and recurrent asthma (Tullis, 1970; Dunlap *et al.* 1984).

Hyperinfection syndrome/disseminated infections

Hyperinfection describes the syndrome of accelerated autoinfection, generally – although not always (Husni *et al.* 1996; Tiwari *et al.* 2012; Dogan *et al.* 2014) – the result of an alteration in immune status. The distinction between autoinfection and hyperinfection is quantitative and not strictly defined. Therefore, hyperinfection syndrome implies the presence of signs and symptoms attributable to increased larval migration. Development or exacerbation of gastrointestinal and pulmonary symptoms is seen, and the detection of increased numbers of larvae in stool and/or sputum is the hallmark of hyper-infection. Larvae in non-disseminated hyperinfection are increased in numbers but confined to the organs normally involved in the pulmonary autoinfective cycle (i.e. gastrointestinal tract, peritoneum and lungs), although enteric bacteria, that can be carried by the filariform larvae or gain systemic access through intestinal ulcers, may affect any organ system.

The term disseminated infection is often used to refer to migration of larvae to organs beyond the range of the pulmonary autoinfective cycle. This does not necessarily imply a greater severity of disease. Extra-pulmonary migration of larvae has been shown to occur routinely during the course of chronic *S. stercoralis* infections in experimental dogs (Schad *et al.* 1989) and has been reported to cause symptoms in humans without other manifestations of hyperinfection syndrome (Lai *et al.* 2002). Similarly, many cases of hyperinfection are fatal without larvae being detected outside the pulmonary autoinfective route.

General features

The clinical manifestations of *S. stercoralis* hyperinfection vary widely. The onset may be acute (Thomas and Costello, 1998) or insidious (Wurtz *et al.* 1994). Fever and chills are not uniformly present and should prompt a search for an associated bacterial infection. Other constitutional symptoms include fatigue (Liepman, 1975), weakness (Chu *et al.* 1990) and total body pain (Chaudhuri *et al.* 1980). Blood counts performed during hyperinfection may

show eosinophilia but more often show a suppressed eosinophil count (Grove, 1996). Patients who have increased peripheral eosinophilia during hyperinfection appear to have a better prognosis (Jamil and Hilton, 1992).

Gastrointestinal manifestations

Gastrointestinal symptoms are common but are non-specific. Some case reports do not mention any gastrointestinal symptoms (Liepman, 1975). Abdominal pain (Celedon *et al.* 1994), often described as crampy or bloating in nature, watery diarrhoea, constipation anorexia, weight loss (Scowden *et al.* 1978), difficulty swallowing (Yee *et al.* 1987), sore throat, nausea (Liepman, 1975), vomiting and gastrointestinal bleeding, and small bowel obstruction (Newton *et al.* 1992; Thomas and Costello, 1998) may result, with diffuse abdominal tenderness and hypoactive bowel sounds. Protein-losing enteropathy may give rise to acute or worsening hypoalbuminaemia with peripheral oedema (Ho *et al.* 1997; Yoshida *et al.* 2006) or ascites (Liepman, 1975). Hypokalaemia (Jain *et al.* 1994) or other electrolyte abnormalities may reflect these gastrointestinal disturbances. Direct stool exam usually shows numerous rhabditiform and filariform larvae. Occasionally, adult worms (Ho *et al.* 1997) and eggs (Armignacco *et al.* 1989; Cahill and Shevchuk, 1996) are also seen. Occult or gross blood is a common finding. Esophagitis and gastritis are reported, in addition to duodenitis, jejunitis, ileitis, colitis, including pseudomembranous colitis and proctitis. Mucosal ulceration is most common in the small intestine, but can occur at any level from the oesophagus (Levi *et al.* 1997) and stomach (Wurtz *et al.* 1994) to the rectum. Larvae may be seen in these ulcers on biopsy (Gompels *et al.* 1991; Wurtz *et al.* 1994; Ho *et al.* 1997). Crypts are often distorted by the numerous larvae (Wurtz *et al.* 1994) Inflammatory infiltrates (Mori *et al.* 1998) or areas of necrosis (Neefe *et al.* 1973; Yee *et al.* 1987) in involved intestinal mucosa may be present (Newton *et al.* 1992). The appendix may also be invaded by larvae (Scowden *et al.* 1978; Kramer *et al.* 1990). Abdominal imaging may show small bowel distension with air-fluid levels (Newton *et al.* 1992; Celedon *et al.* 1994). Mucosal oedema (Neefe *et al.* 1973; Mori *et al.* 1998) and findings consistent with protein-losing enteropathy may also be demonstrated radiographically. Computed tomography scans can occasionally reveal intra-abdominal lymphadenopathy (Thomas and Costello, 1998).

Cardiopulmonary manifestations

Cardiopulmonary manifestations range from none at all to cough (Nomura and Rekrut, 1996), wheezing (Kramer *et al.* 1990), (Yee *et al.* 1987), a choking sensation (Cahill and Shevchuk, 1996), hoarseness (Yee *et al.* 1987), chest pain (Chaudhuri *et al.* 1980; Cahill and Shevchuk, 1996), haemoptysis, palpitations, atrial fibrillation (Gordon *et al.* 1994), dyspnoea (Nomura and Rekrut, 1996), and, rarely, respiratory collapse. Respiratory alkalosis is common (Thompson and Berger, 1991). Pneumothorax is rarely seen (McNeely *et al.* 1980). Sputum may demonstrate filariform or rhabditiform larvae and even, occasionally, eggs (Kennedy *et al.* 1989). These findings suggest that filariform larvae develop into adults in the lungs, and a new generation of rhabditiform larvae is produced locally (Cirioni *et al.* 1996). This hypothesis is supported by reports of adult parasites being expectorated post treatment (McLarnon and Ma, 1981) and autopsy studies showing adult worms in lung tissue (Cahill and Shevchuk, 1996). Chest imaging most frequently show bilateral or focal interstitial

infiltrates. Lung tissues may show alveolar haemorrhage. Petechial haemorrhage or hyperaemia of the bronchial, tracheal and laryngeal mucosa has also been reported (Yee *et al.* 1987; Cahill and Shevchuk, 1996).

Dermatologic manifestations

Pruritic linear streaks of the lower trunk, thighs and buttocks (*larva currens*) frequently accompany hyperinfection (Ho *et al.* 1997). Petechial and purpuric rashes of these same areas, in which larvae have been demonstrated on skin biopsy is common (Ronan *et al.* 1989; Stewart *et al.* 2011). Skin manifestations of vasculitis (Harcourt-Webster *et al.* 1991) or of disseminated intravascular coagulation seen associated with Gram-negative sepsis (Neefe *et al.* 1973) may, of course, also present during hyperinfection.

Central nervous system (CNS) manifestations

Meningeal signs and symptoms (Kramer *et al.* 1990) are the most common manifestation of CNS involvement in hyperinfection syndrome. Hyponatremia may accompany meningitis (Harcourt-Webster *et al.* 1991; Jain *et al.* 1994). In patients with meningitis, spinal fluid may show parameters of aseptic meningitis [i.e. pleocytosis, elevated protein, normal glucose, negative bacterial cultures (Scowden *et al.* 1978; Vishwanath *et al.* 1982)] or demonstrate characteristics of a Gram-negative bacterial infection. Larvae have been found in spinal fluid (Dutcher *et al.* 1990), meningeal vessels (Cahill and Shevchuk, 1996), dura, epidural, subdural and subarachnoid spaces (Neefe *et al.* 1973). Eosinophilic meningitis has not been reported.

Sepsis—Hyperinfection syndrome/disseminated are often complicated, and rarely preceded by infections caused by gut flora that gain access to extrain-testinal sites, presumably through ulcers induced by the filariform larvae or by virtue of being carried on the surface or in the intestinal tract of larvae themselves. Organisms that have been reported to cause sepsis in such patients include Group D *Streptococci, Candida Streptococcus bovis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas, Enterococcus faecalis*, coagulase negative *staphylococci* and *Streptococcus pneumoniae*. Polymicrobial infections can also occur (Link and Orenstein, 1999).

Disseminated infections

Organs to which larvae have disseminated include skin, mesenteric lymph nodes, gallbladder, liver, diaphragm, heart, pancreas, skeletal muscle, kidneys, ovaries and brain (Keiser and Nutman, 2004) based largely on autopsy studies. Chronic inflammation or necrosis frequently surrounds the larvae, but tissue reactions are also frequently absent (Neefe *et al.* 1973; Takayanagui *et al.* 1995).

Conditions associated with hyperinfection syndrome and dissemination (Table 1)

Corticosteroids and other agents—Corticosteroids (most commonly prednisone and methyl-prednisilone) have a particularly strong and specific association with the development of hyperinfection syndrome and dissemination. Beyond their known (and broad) effects on the host immune system, it has been postulated that corticosteroids have a

direct effect on the *S. stercoralis* parasite (Genta, 1992; Ramanathan *et al.* 2011) though this has not been shown definitively. Other immunosuppressive therapies and underlying conditions (Table 1) may also predispose to dissemination. However, the concomitant administration of corticosteroids in most of these other conditions makes it difficult to assign a direct causal association. Hyperinfection syndrome has been described regardless of dose, duration or route of administration of corticosteroids. Even short courses (6–17 days) of corticosteroids in immunocompetent patients without underlying immunosuppressive conditions have even been associated with hyperinfection syndrome and death (Ghosh and Ghosh, 2007).

HTLV-1 Infection—Human T-cell lymphotropic virus type 1 (HTLV-1) represents a significant risk factor for the development of hyperinfection syndrome or disseminated strongyloidiasis (Carvalho and Da Fonseca Porto, 2004) that may be related to HTLV-I driven alterations in IgE or associated Type-2 responses (Neva *et al.* 1998; Porto *et al.* 2001; Mitre *et al.* 2003; Santos *et al.* 2004). A growing body of evidence points to the synergistic relationship between HTLV-1 and *S. stercoralis*. Higher rates of *S. stercoralis* infection have been found in HTLV-1 patients (Carvalho and Da Fonseca Porto, 2004). *Strongyloides stercoralis* infection has been shown to influence the natural history of HTLV-1 infection (Marcos *et al.* 2011) and has been considered a co-factor in the development of HTLV-1-associated diseases (Gotuzzo *et al.* 2000).

HIV—Strongyloidiasis was once considered an AIDS defining illness (Keiser and Nutman, 2004) yet there is no evidence that a low CD4 count will increase the risk of dissemination or decrease the chance of clearing an infection (Walson *et al.* 2010). Severe infection with *Strongyloides* has not been observed frequently with HIV-infected patients (Celedon *et al.* 1994). Hyperinfection syndrome is associated with the use of corticosteroids in the treatment of immune reconstitution inflammatory syndrome (IRIS) (Brown *et al.* 2006; Mascarello *et al.* 2011). Whether IRIS occurs after the initiation of antiretroviral therapy in patients with single infections with *S. stercoralis* remains unclear.

***Strongyloides* infection in the transplanted patient—**Solid organ transplants (Stone and Schaffner, 1990; Lichtenberger *et al.* 2009; Mokaddas *et al.* 2009) haematopoietic stem cell transplants (HSCT) and their pre-conditioning regimens and subsequent immunosuppression have been linked to dissemination of *S. stercoralis*. Among the different types of transplants, HSCT has the highest incidence of fatal dissemination with a higher mortality than in other types of transplants (Wirk and Wingard, 2009). A unique complication of transplants is the development of graft *vs* host disease (GVHD). In HSCT the risk of GVHD is greater than for other types of transplants because of the use of allogeneic stem cells (non-ablative conditioning). Because the main therapy for acute GVHD is corticosteroids, it is at the time that steroids are given in the setting of chronic strongyloidiasis that the risk for dissemination is high (Choi and Reddy, 2014).

The geographical proximity to either North America or Europe by immigrants from Central and South America and Africa that are being transplanted are a sizeable ‘at risk’ population for dissemination of *S. stercoralis* (Wolfe *et al.* 2010; Guermani *et al.* 2013). Organ donors

have also been shown to transmit *Strongyloides* infection with cases of solid organ transplant-associated *S. stercoralis* infections having been reported (Weiser *et al.* 2011).

Other—Several case reports have supported an association between *S. stercoralis* infection hypogammaglobulinaemia associated with multiple myeloma and nephrotic syndrome (Seet *et al.* 2005; Hsieh *et al.* 2006; Yassin *et al.* 2010).

HUMAN IMMUNE RESPONSES AND PROTECTIVE IMMUNITY

The human immune response to *S. stercoralis* has not been studied in great detail. Most of our knowledge about immune responsiveness and protective immunity has come from animal studies [reviewed in this issue (Breloer and Abraham, 2016)]. These studies, that have as an added benefit the knowledge of exactly when the infection was initiated, have suggested a role for antibodies (of many isotypes) as well as for innate and adaptive immune responses in mediating resistance to infection (Fig. 1).

In humans, it has been shown, however, that Th2 response are essential to protect against hyperinfection (Porto *et al.* 2001; Iriemenam *et al.* 2010) and that individuals with strongyloidiasis develop *S. stercoralis*-specific antibodies of the IgM, IgG, IgA and IgE isotypes (McRury *et al.* 1986; Genta and Lillibridge, 1989; Atkins *et al.* 1997; Rodrigues *et al.* 2007).

The evolution of the antibody response in *S. stercoralis* infection has been difficult to discern given that only cross-sectional studies of infected people have been performed. Nevertheless, these studies of *S. stercoralis* infection have suggested that there is rapid induction of parasite-specific IgE, IgG1, IgG2 and IgG3 antibodies directed against crude *S. stercoralis* soluble extracts that is followed (often weeks to months later) with a rise in parasite-specific IgG4. In that the IgE and IgG4 antibodies often are directed at a similar, but restricted, set of antigens (Genta and Lillibridge, 1989), it is the IgG4 antibodies that allow for the blocking of IgE-mediated effector responses (Genta *et al.* 1983; Barrett *et al.* 1988; Genta and Lillibridge, 1989) thereby modulating some of the Type-2-mediated inflammation.

Recent work has suggested that once *S. stercoralis* establishes patency [usually within 6–7 weeks following infection (Freedman, 1991)] that the infection drives a systemic cytokine response that is dominated by Th2-associated and anti-inflammatory cytokines (Anuradha *et al.* 2015*a*) (Fig. 1). This systemic response appears to reflect an expansion of antigen-specific Th2/Th9 cells with a concomitant contraction of Th1 and Th17 cells, the latter being dependent on IL-10 (George *et al.* 2014; Anuradha *et al.* 2016, 2015*b*). With appropriate anthelmintic therapy leading to cure of the *S. stercoralis* infection, many of these cytokine levels and T-cell perturbations return to their homeostatic state (Anuradha *et al.* 2015*a*, *b*).

Like many other systemic helminth infections (e.g. *Schistosoma mansoni, Wuchereria bancrofti*), *S. stercoralis* also, given its capacity for chronic longstanding infection, can modulate responses to bystander antigens particularly in the context of infection with other pathogens such as *Mycobacterium tuberculosis* (George *et al.* 2015) and HTLV-1 (Mitre *et al.* 2003; Montes *et al.* 2009; Salles *et al.* 2013).

DIAGNOSIS

For the chronically infected, asymptomatic individual, diagnosis of strongyloidiasis can be challenging (Levenhagen and Costa-Cruz, 2014; Buonfrate *et al.* 2015; Toledo *et al.* 2015). Diagnosis of hyper-infection syndrome/disseminated *S. stercoralis* infection is much less difficult given the large numbers of larvae often seen in the stool or other bodily fluids including CSF, pleural fluid, bronchoalveolar lavage fluid.

Parasitological methods

Definitive diagnosis relies on detection of larvae in the stool. However, intermittent and scanty excretion of larvae limits the utility of standard stool studies. Various investigators have attempted to improve the diagnostic yield of stool examination using techniques such as direct smear of feces in saline/Lugol's iodine stain, Baermann concentration, Harada-Mori filter paper culture, quantitative formalin ethyl acetate concentration technique and nutrient agar plate cultures [see (Sato *et al.* 1995)]. Sensitivity improved to 100% when seven stool samples were studied (Siddiqui and Berk, 2001). Duodenal aspiration, while more sensitive than stool examination, is an invasive procedure that makes it a less favourable option. Duodenal biopsy, when performed, can demonstrate parasites nested in the gastric crypts or duodenal glands, as well as eosinophil infiltration of the lamina propria (Rivasi *et al.* 2006).

Immunological methods

Antibody detection—A number of immunoassays, most notably enzyme-linked immunosorbent assays (ELISAs), have been increasingly used in conjunction with stool studies to increase diagnostic sensitivity. The high negative predictive value of these immunoassays can be particularly useful in excluding *S. stercoralis* infection as part of the differential diagnosis. Despite their utility, antibody-based immunoassays have several limitations including: (1) cross-reactivity in patients with active filarial infections; (2) lower sensitivity in patients with haematologic malignancies or HTLV-1 infection; and (3) the inability to distinguish between current and past infection. Moreover, the current available immunoassays [see (Levenhagen and Costa-Cruz, 2014; Buonfrate *et al.* 2015; Toledo *et al.* 2015) for a comprehensive discussion] relies on the preparation of *S. stercoralis* larval antigen from stool samples of heavily infected humans or experimentally infected animals or from related(but not *S. stercoralis*) *Strongyloides* species (e.g. *S. ratti*).

To overcome some of these drawbacks, *S. stercoralis*-specific recombinant antigens, such as NIE (Ravi *et al.* 2002) and SsIR (Ramachandran *et al.* 1998), were proposed as alternatives to the crude antigen-based immunoassays currently in use. Using a number of formats including ELISA [(Krolewiecki *et al.* 2010), luciferase immunoprecipitation systems (Ramanathan *et al.* 2008; Krolewiecki *et al.* 2010; Bisoffi *et al.* 2014)] and diffraction-based biosensors (Pak *et al.* 2014) the use of recombinant NIE and/or SsIR has improved greatly the diagnostic accuracy and utility of these antibody-based assays (Bisoffi *et al.* 2014; Levenhagen and Costa-Cruz, 2014; Buonfrate *et al.* 2015; Toledo *et al.* 2015).

Antigen detection—Coproantigen detection assays have the ability to overcome some of the limitations seen in immunoassays that measure antibody (see above). There have been several capture ELISA assays developed for *S. stercoralis* coproantigen detection (El-Badry, 2009; Sykes and McCarthy, 2011), and both of these assays have been performed on relatively few samples and are only available in a research setting.

Molecular diagnosis—Molecular diagnostics – using standard (and/or nested-) PCR, qPCR or loop-mediated isothermal amplification assays – have been increasingly gaining traction for use stool-based assays given their high degree of specificity and sensitivity (ten Hove *et al.* 2009; Verweij *et al.* 2009; Taniuchi *et al.* 2011; Mejia *et al.* 2013; Sultana *et al.* 2013; Watts *et al.* 2014; Easton *et al.* 2016; Llewellyn *et al.* 2016). Indeed, the improved specificity relies on the specific DNA targets used [18S rRNA, IST1, cytochrome *c* oxidase subunit 1 or the highly repetitive interspersed repeat sequence (Moore *et al.* 1996)] and the improved sensitivity has resulted from better methods for DNA extraction in stool (ten Hove *et al.* 2009; Taniuchi *et al.* 2011; Liu *et al.* 2013; Mejia *et al.* 2013; Sultana *et al.* 2013; Easton *et al.* 2016). These molecular diagnostic techniques likely identify active *S. stercoralis* infection as positivity has been shown to be lost following definitive treatment.

TREATMENT

The goals for therapy for *S. stercoralis* infection are to: (1) clear the organism completely thereby eliminating the possibility of autoinfection: (2) treat symptomatic infection; and (3) prevent complications associated with asymptomatic infection. Oral ivermectin (200 μg kg^{-1} for 2 days) remains the treatment of choice for uncomplicated *S. stercoralis* infections (Keiser and Nutman, 2004; Suputtamongkol *et al.* 2011; Mejia and Nutman, 2012; Toledo *et al.* 2015; Henriquez-Camacho *et al.* 2016) as it targets both adults and larvae. Albendazole at 400 mg twice a day for 3–7 days has been shown to be slightly less effective than ivermectin for the treatment of uncomplicated *S. stercoralis* (Suputtamongkol *et al.* 2011; Henriquez-Camacho *et al.* 2016) and should be considered an alternative therapy. This is likely because albendazole primarily targets only the adult parasites. Thiabendazole (25 mg kg^{-1} day^{-1}) for three days can also be used, but because of gastrointestinal side effects, its use has been supplanted by ivermectin.

Hyperinfection syndrome should be considered a potential medical emergency. Thus, treatment should be started immediately if this diagnosis is being considered. Although no controlled trials have been performed in hyperinfection syndrome, daily ivermectin has been the *de facto* treatment with the length of treatment being for a minimum of 2 weeks (and often until there has been evidence of two full weeks of negative stool examination). Reduction of immunosuppressive therapy should also be an important part of treatment, but obviously needs to be weighed against long-term outcomes of the underlying condition. There have been case reports of the improved efficacy of combination treatment with ivermectin and albendazole (Pornsuriyasak *et al.* 2004) but no randomized trials have been done.

Other methods of ivermectin administration may have to be used, particularly when patients are unable to take oral medication (even through a nasogastric tube) because of severe

systemic illness or paralytic ileus. These include per rectal and parenteral formulations (Grein *et al.* 2010). The parenteral formulation is a veterinary formulation of ivermectin and should be reserved for extreme situations with no other options for clearing the *Strongyloides* infection (Marty *et al.* 2005; Salluh *et al.* 2005; Turner *et al.* 2005; Suputtamongkol *et al.* 2008; Lichtenberger *et al.* 2009; Marcos *et al.* 2011; Moura *et al.* 2012; Donadello *et al.* 2013; Barrett *et al.* 2016).

In conclusion, the gaps in our understanding of human strongyloidiasis, among the most neglected of the neglected tropical diseases (NTDs) (Olsen *et al.* 2009) are extraordinary given the rapid pace of scientific and clinical advances seen in related areas of parasitic and other tropical infectious diseases. Given its increasing importance as a significant public health problem (in high-, middle- and low-income countries) and the lack of a public health response (Krolewiecki *et al.* 2013), harnessing the insights made, to date, in our understanding of the basic biology and genetic makeup of *Strongyloides* (Hunt *et al.* 2016), the host response to this long-lived parasite (Breloer and Abraham, 2016), and molecularly based approaches to diagnosis and intervention must be made an imperative if we are to consider a world free of soil transmitted helminths (of which *S. stercoralis* is one of the most important).

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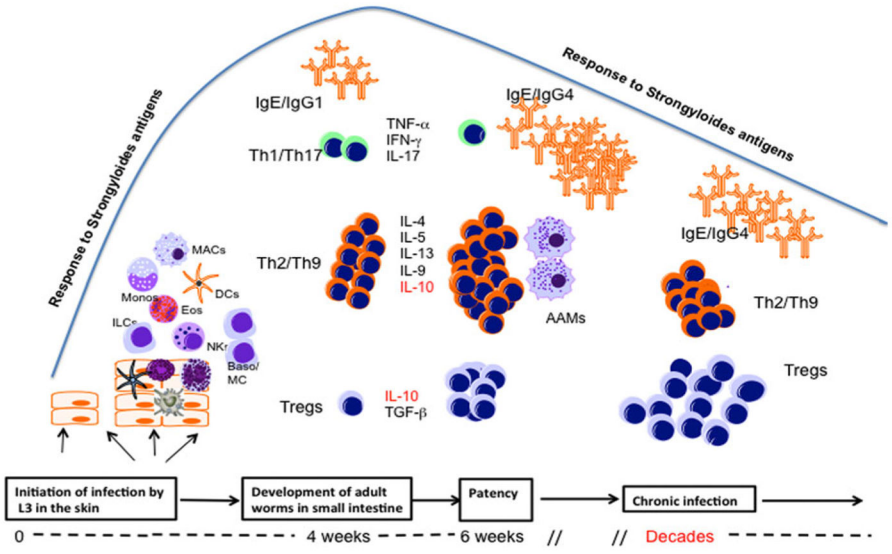

Fig. 1.

Immune responses in *Strongyloides stercoralis* infection as a function of time after infection initiation. The infective L3 larval parasites initiate infection at skin sites and activate a variety of different cell types such as innate lymphoid cells (ILCs), macrophages (MAC), dendritic cells (DCs), natural killer cells (NK), eosinophils (Eos) and basophils/mast cells (Baso/MC). At this relatively early phase of infection (or by the time the adult worms are established in the small intestine) the parasite induces the differentiation of a small number of effector Th1/Th17 and a relatively larger number of Th2 cells which together with IgE antibody, may lead to attrition of some of the parasites. At the time of patency (when larval production occurs) there is an expansion of Th2/Th9 $CD4^+$ cells, a further contraction of Th1/Th17 cells and the induction of alternatively activated macrophages (AAM). With the evolution of chronic longstanding infection, there is an associated expansion of IL-10- and/or TGFβ-producing regulatory T cells (Tregs) and a small contraction of Th2/Th9 cells.

Table 1

Conditions associated with hyperinfection syndrome

Drugs/biologics
Immunosuppressives
Corticosteroids
Azathioprine
Cyclophosphamide
Methotrexate
Anti-neoplastic agents
6-mercaptopurine
Adriamycin
Bleomycin
Carmustine
Chlorambucil
Doxorubicin
Daunorubicin
Ifosfamide
Melphalan
Mitoxantrone
VP16
Vinca alkaloids
Biologics
Etanercept
Inflixumab
Rituximab
Antithymocyte globulin
Anti-CD3 (OKT3)
Mycophenolate mofetil
Total body irradiation
Diseases/syndromes
HTLV-1
Hypogammaglobulinaemia (nephrotic syndrome and multiple myeloma)
Haematologic malignancies and myelodysplastic syndromes
Solid Organ Transplantation
HSCT
HIV/IRIS
Malnutrition